EXHIBIT B

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
PIHONAK, SARAH	
ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
11/29/2012	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	12/835,964	WOOLLAM, GRAHAME	
	Examiner	Art Unit	
	SARAH PIHONAK	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 September 2012*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1-20* is/are pending in the application.

5a) Of the above claim(s) *19 and 20* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-18* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/14/2010;9/21/2010*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

Priority

This application, filed on 7/14/2010, claims priority to provisional appl. 61/225803, filed on 7/15/2009. The effective U.S. filing and priority date of the claims is 7/15/2009.

Response to Restriction Requirement

1. Applicant's election without traverse of the invention of Group I, claims 1-18 in the reply filed on 9/13/2012 is acknowledged.

2. Claims 19-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 9/13/2012.

3. Claims 1-18 were examined.

4. Claims 1-18 are rejected.

Claim Rejections-35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-6, 12-16, and 18 are rejected under 35 U.S.C. 102(b) as anticipated by Mammen et. al., US Patent Publ. 2005/0203133 (cited in the IDS).

The claims are directed to a crystalline free base of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester characterized by a powder x-ray diffraction comprising diffraction peaks at 2θ values of 6.6±0.1, 13.1±0.1, 18.6±0.1, 19.7±0.1, and 20.2±0.1. The claims are also directed to a process for preparing the crystalline freebase form III of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester, comprising contacting biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester with acetonitrile.

Mammen et. al. discloses biphenyl muscarinic receptor antagonists, pharmaceutical compositions, and processes for preparing the muscarinic receptor antagonists (Abstract; p. 1, paragraph [0003]; p. 1, paragraph [0009]-p. 2, paragraph [0030]). The biphenyl muscarinic antagonists exhibit high potency for the treatment of pulmonary disorders and have reduced systemic side effects (p. 1, paragraphs [0003], [0006], and [0008-0009]). Mammen et. al. discloses biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester (p. 6, paragraphs [0106-0107]; pp. 20-21, paragraphs [0295-0296]). Mammen et. al. discloses a process of preparing a freebase crystalline biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester which comprises contacting biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester with acetonitrile (p. 21,

paragraph [0304]-p. 22, paragraph [0305]; p. 22, see Ex. 1E, paragraphs [0307-0308]). Mammen et. al. discloses a pharmaceutical composition comprised of the biphenyl compound and a pharmaceutically acceptable carrier (p. 2, paragraph [0031]), as well as a pharmaceutical composition comprised of the biphenyl muscarinic antagonist, a $ß_2$ adrenergic receptor agonist, and a steroidal anti-inflammatory agent (p. 15, paragraph [0241]; pp. 35-36, claim 1; pp. 36-37, claim 13; p. 37, claims 15-17). Mammen et. al. discloses the biphenyl compound in micronized form (p. 13, paragraph [0226]; p. 16, paragraphs [0251-0252]). While Mammen et. al. does not explicitly disclose freebase crystalline biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester as having diffraction peaks at 2θ values of 6.6±0.1, 13.1±0.1, 18.6±0.1, 19.7±0.1, and 20.2±0.1, the instantly claimed process of preparing freebase crystalline biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester is the same as the method disclosed by Mammen et. al., as both methods comprise contacting biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester with acetonitrile. It would have been expected that, without sufficient evidence to the contrary, the freebase crystalline biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester disclosed by Mammen et. al. was the same as the freebase crystalline form III of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester as instantly claimed, as both compounds are prepared by the same method. It would

therefore have been expected that freebase crystalline biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester as disclosed by Mammen et. al. would have been characterized by a powder x-ray diffraction comprising diffraction peaks at 2θ values of 6.6±0.1, 13.1±0.1, 18.6±0.1, 19.7±0.1, and 20.2±0.1, as well as the diffraction peaks cited in instant claims 2 and 3, because a compound and its properties are not patentably distinguishable. See MPEP 2141.02, where it is stated that, "From the standpoint of patent law, a compound and all its properties are inseparable"; *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963). Additionally, as Mammen et. al. discloses the same method of preparing crystalline freebase biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester and thus discloses form III of crystalline freebase biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester, other characteristics of the compound, such as the powder x-ray diffraction pattern as shown in Fig. 1; the differential scanning calorimetry thermogram as shown in Fig. 4; and a melting point of about 125 ℃, would have also have been expected to have existed in the crystalline freebase biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester disclosed by Mammen et. al. Mammen et. al. discloses the preparation of crystalline freebase biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester of claim 1 and thus discloses a process of purifying biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester.

Claim Rejections-35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. Claims 1, 7-11, and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mammen et. al., US Patent Publ. 2005/0203133 (cited in the IDS).

The claims are directed to a crystalline free base of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester characterized by a powder x-ray diffraction comprising diffraction peaks at 2θ values of 6.6±0.1, 13.1±0.1, 18.6±0.1, 19.7±0.1, and 20.2±0.1. The claims are also directed to a process of preparing the crystalline freebase form IV of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester comprising the following steps: a) forming a seed crystal of the crystalline freebase form

III; b) dissolving the crystalline freebase form III in acetonitrile to form a solution; c) adding the seed crystal to the solution.

Mammen et. al. discloses biphenyl muscarinic receptor antagonists, pharmaceutical compositions, and processes for preparing the muscarinic receptor antagonists (Abstract; p. 1, paragraph [0003]; p. 1, paragraph [0009]-p. 2, paragraph [0030]). The biphenyl muscarinic antagonists exhibit high potency for the treatment of pulmonary disorders and have reduced systemic side effects (p. 1, paragraphs [0003], [0006], and [0008-0009]). Mammen et. al. discloses biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester (p. 6, paragraphs [0106-0107]; pp. 20-21, paragraphs [0295-0296]). Mammen et. al. teaches a process of preparing crystalline freebase biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester which comprises preparing a seed crystal of freebase biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester; adding the seed crystal to a solvent composition comprising acetonitrile; and forming a solution by dissolving crystalline freebase in a solvent composition comprising acetonitrile (pp. 21-22, paragraphs [0304-0306]). While Mammen et. al. does not explicitly teach the order of steps (a)-(c), all of these steps are taught to be carried out in the preparation of crystalline freebase biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester. Furthermore, the selection of any order of performing process steps taught by the prior art would have been prima facie obvious to a skilled artisan in the absence or new or unexpected results; see

MPEP 2144.04, *In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946). Thus, as Mammen et. al. discloses a process of preparing crystalline freebase biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester which comprises steps a), b), and c) as cited in instant claim 17, it would have been prima facie obvious to one of ordinary skill in the art that the product resulting from these steps would have comprised crystalline freebase form IV biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester, as the instantly claimed process of preparing crystalline freebase form IV biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester also comprises process steps a), b), and c). It would have been prima facie obvious that crystalline freebase form IV biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester as taught by Mammen et. al. would have been characterized by a powder x-ray diffraction comprising diffraction peaks at 2θ values of 6.6±0.1, 13.1±0.1, 18.6±0.1, 19.7±0.1, and 20.2±0.1; the additional diffraction peaks as cited in instant claims 7 and 8; the x-ray diffraction pattern as shown in Fig. 2; the differential scanning calorimetry thermogram as shown in Fig. 5; and a melting point of about 119 ℃, as a compound and its properties are not patentably distinguishable. See MPEP 2141.02, where it is stated that, “From the standpoint of patent law, a compound and all its properties are inseparable”; *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963). It would have been prima facie obvious that as Mammen et. al. teaches steps a), b), and c) of preparing

crystalline freebase biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester, the product resulting from these steps would have been crystalline freebase form IV of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester and thus would have had the same characteristics and properties of form IV as cited in the instant claims.

10. Claims 1-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Axt et. al., WO 2006/099165 (provisional appl. Filing date 3/10/2005; publication date 9/21/2006).

The claims are directed to a crystalline free base of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester characterized by a powder x-ray diffraction comprising diffraction peaks at 2θ values of 6.6±0.1, 13.1±0.1, 18.6±0.1, 19.7±0.1, and 20.2±0.1. The claims are also directed to a process of preparing the crystalline freebase form III of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester which comprises contacting freebase biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester with acetonitrile; and a process of preparing crystalline freebase form IV of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester comprising the following steps:

a) forming a seed crystal of the crystalline freebase form III; b) dissolving the crystalline freebase form III in acetonitrile to form a solution; c) adding the seed crystal to the solution.

Axt et. al. teaches crystalline forms of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester, methods of preparing the crystalline forms, and a pharmaceutical composition comprised of a crystalline form (Abstract; p. 1, lines 5-10 and lines 18-24). Freebase crystalline forms of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester are taught (p. 2, lines 10-14; p. 3, lines 27-32). Axt et. al. teaches biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester as a muscarinic antagonist which is used therapeutically for the treatment of pulmonary disorders (p. 1, lines 12-17; p. 3, lines 13-26; p. 27, lines 3-15). A method of preparing a crystalline freebase of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester comprising forming a seed crystal of crystalline freebase biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester; dissolving a crystalline freebase form of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester in an inert diluent; and adding the seed crystal to the solution is taught (p. 11, lines 8-11), as well as adding the ester compound to a solvent comprising acetonitrile (p. 10, line 32-p. 11, line 7). A solution of water: acetonitrile is exemplified as a diluent for preparation of the crystalline freebase

form (p. 11, lines 12-23). A pharmaceutical composition comprised of crystalline freebase biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester, a pharmaceutically acceptable carrier, a $ß_2$ adrenergic agonist, and an anti-inflammatory steroidal agent is taught (p. 21, lines 14-24). Micronized crystalline freebase biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester is taught (p. 4, lines 1-3; p. 17, lines 14-16). Axt et. al. teaches the preparation of a crystalline form of freebase biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester which is characterized by having 2 or more diffraction peaks at 2θ values such as 16.7±0.2, 17.4±0.2, 18.5±0.2, 19.4±0.2, 20.8±0.2, and 21.4±0.2 (p. 13, lines 4-7); these peaks also overlap with several of the diffraction peaks cited in instant claims 1-3, 7, and 8.

Axt et. al. discloses a process of preparing crystalline freebase biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester which comprises contacting freebase biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester with acetonitrile, as well as steps a), b), and c) as cited in instant claim 17. It would have been prima facie obvious to one of ordinary skill in the art that the products resulting from these steps would have comprised crystalline freebase form III and IV of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester, as the instantly claimed process of preparing crystalline freebase forms III and IV of biphenyl-

2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester also comprises contacting freebase biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester with acetonitrile (to prepare form III) and process steps a), b), and c) (to prepare form IV). It would have been prima facie obvious that crystalline freebase form III of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester as taught by Axt et. al. would have been characterized by a powder x-ray diffraction comprising diffraction peaks at 2θ values of 6.6±0.1, 13.1±0.1, 18.6±0.1, 19.7±0.1, and 20.2±0.1; the diffraction peaks as cited in claims 2 and 3 for form III; the x-ray diffraction pattern as shown in Fig. 1; the differential scanning calorimetry thermogram as shown in Fig. 4; and a melting point of about 125 °C, as a compound and its properties are not patentably distinguishable. See MPEP 2141.02, where it is stated that, “From the standpoint of patent law, a compound and all its properties are inseparable”; *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963). Furthermore, as crystalline form IV of freebase biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester would have been prima facie obvious in view of the method taught by Axt et. al., the characteristics of form IV, such as the diffraction peaks cited in claims 7 and 8; the powder x-ray diffraction pattern shown in Fig. 2; the differential scanning calorimetry thermogram as shown in Fig. 5; and a melting point of about 119 °C, would have been expected to have been present along with the compound, as such characteristics are

properties of crystalline freebase form IV. Axt et. al. teaches the preparation of crystalline freebase biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester and thus teaches a process of purifying biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester.

Claim Rejections-Obviousness Type Double Patenting

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422

F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. Claims 1-18 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 3-5 of U.S. Patent No. 7,585,879. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims encompass crystalline freebase biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester. The claims of the US patent are directed to the compound biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester and a pharmaceutical composition comprised of the compound. While the claims of the US patent do not explicitly cite the compound in crystalline form, the disclosure of USP 7,585,879 teaches biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester to exist as a freebase crystal

(column 38, Ex. 1D, lines 1-35); thus, it would have been obvious that the claims of the US patent would have encompassed crystalline forms of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester. The instant claims and claims of the US patent are therefore not patentably distinct from each other.

13. **Claims 1-18 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 and 12-30 of U.S. Patent No. 7,803,812**. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims encompass a pharmaceutical composition comprised of crystalline freebase biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester with a pharmaceutically acceptable carrier. While the claims of the US patent do not explicitly cite the compound in crystalline form, the disclosure of USP 7,803,812 teaches biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester to exist as a freebase crystal (column 36, Ex. 1D, lines 20-49); thus, it would have been obvious that the claims of the US patent would have encompassed crystalline forms of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester. The instant claims and claims of the US patent are therefore not patentably distinct from each other.

14. **Claims 1-18 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 8,273,894.** Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims encompass a pharmaceutical composition comprised of crystalline freebase biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester, a ß$_2$ adrenergic agonist, and an anti-inflammatory steroidal agent with a pharmaceutically acceptable carrier. While the claims of the US patent do not explicitly cite the compound in crystalline form, the disclosure of USP 8,273,894 teaches biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester to exist as a freebase crystal (column 36, Ex. 1D, line 50-column 37, line 15); thus, it would have been obvious that the claims of the US patent would have encompassed crystalline forms of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester. The instant claims and claims of the US patent are therefore not patentably distinct from each other.

15. **Claims 1-18 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 8,034,946.** Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims encompass a pharmaceutical composition

comprised of crystalline freebase biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester with a pharmaceutically acceptable carrier. While the claim of the US patent does not explicitly cite the compound in crystalline form, the disclosure of USP 8,034,946 teaches biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester to exist as a freebase crystal (column 37, Ex. 1D, line 36-column 38, line 16); thus, it would have been obvious that claim 1 of the US patent would have encompassed crystalline forms of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester. The instant claims and claims of the US patent are therefore not patentably distinct from each other.

16. **Claims 1-18 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 7,910,608.** Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims encompass a pharmaceutical composition comprised of crystalline freebase biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester with a pharmaceutically acceptable carrier. While the claims of the US patent do not explicitly cite the compound in crystalline form, the disclosure of USP 7,910,608 teaches biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-

ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester to exist as a freebase crystal (column 37, Ex. 1D, line 30-column 38, line 11); thus, it would have been obvious that the claims of the US patent would have encompassed crystalline forms of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester. The instant claims and claims of the US patent are therefore not patentably distinct from each other.

17. **Claim 1-18 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5, 7, and 9-22 of U.S. Patent No. 7,550,595.** Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims encompass a pharmaceutical composition comprised of crystalline freebase biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester with a pharmaceutically acceptable carrier. While the claims of the US patent do not explicitly cite the compound in crystalline form, the disclosure of USP 7,550,595 teaches biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester to exist as a freebase crystal (column 38, Ex. 1D, lines 1-34); thus, it would have been obvious that the claims of the US patent would have encompassed crystalline forms of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester.

The instant claims and claims of the US patent are therefore not patentably distinct from each other.

18. **Claims 1-18 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 13-14 of U.S. Patent No. 7,288,657.** Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims encompass crystalline freebase biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester. While the claims of the US patent do not explicitly cite the compound in crystalline form, the disclosure of USP 7,288,657 teaches biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester to exist as a freebase crystal (column 37, Ex. 1D, line 42-column 38, line 6); thus, it would have been obvious that the claims of the US patent would have encompassed crystalline forms of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester. The instant claims and claims of the US patent are therefore not patentably distinct from each other.

Information Disclosure Statements

19. The information disclosure statements (IDS) submitted on 7/14/2010 and 9/21/2010 were filed and are of record. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner.

Conclusion

20. Claims 1-18 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARAH PIHONAK whose telephone number is (571)270-7710. The examiner can normally be reached on Monday-Thursday 7:00 AM - 5:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SARAH PIHONAK/
Examiner, Art Unit 1627

PATENT
Attorney Docket: P-257-US1
Customer Number 27038

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of Grahame Woollam	
Application No. 12/835,964	Confirmation No. 1229
Filed: July 14, 2010	Group Art Unit 1627
For: CRYSTALLINE FREEBASE FORMS OF A BIPHENYL COMPOUND	Examiner: PIHONAK, Sarah

AMENDMENT UNDER 37 C.F.R. §1.111

Mail Stop Amendment
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Sir:

I. INTRODUCTORY REMARKS

This is in response to the Office Action having a notification date of November 29, 2012. Applicants have carefully considered the Action and respectfully request entry of this amendment and reconsideration of the application in view of the following remarks.

Amendments to the Claims begin on page 2.

Remarks begin on page 5.

II. AMENDMENTS TO THE CLAIMS (WHEN AMEND)

This listing of the claims will replace all prior versions, and listings, of claims in the application.

Claim 1 (Currently amended). A crystalline freebase of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester characterized by a powder x-ray diffraction comprising diffraction peaks at 2θ values of 6.6±0.1, 13.1±0.1, 18.6±0.1, 19.7±0.1, and 20.2±0.1, and selected from Form III having a melting point of about 125°C and Form IV having a melting point of about 119°C.

Claim 2 (Currently amended). The crystalline freebase of Claim 1, wherein Form III is further characterized by having five or more additional diffraction peaks at 2θ values selected from 8.8±0.1, 10.1±0.1, 11.4±0.1, 11.6±0.1, 14.8±0.1, 15.2±0.1, 16.1±0.1, 16.4±0.1, 16.9±0.1, 17.5±0.1, 18.2±0.1, 19.3±0.1, 19.9±0.1, 20.8±0.1, 21.1±0.1, 21.7±0.1, and 22.3±0.1.

Claim 3 (Original). The crystalline compound of Claim 2, characterized by a powder x-ray diffraction pattern comprising diffraction peaks at 2θ values selected from 6.6±0.1, 11.4±0.1, 13.1±0.1, 16.1±0.1, 17.5±0.1, 18.2±0.1, 18.6±0.1, 19.3±0.1, 19.7±0.1, 19.9±0.1, 20.2±0.1, 20.8±0.1, 21.1±0.1, 21.7±0.1, and 22.3±0.1.

Claim 4 (Original). The crystalline compound of Claim 2, further characterized by a powder x-ray diffraction pattern in which the peak positions are substantially in accordance with the peak positions of the pattern shown in FIG. 1.

Claim 5 (Canceled).

Claim 6 (Original). The compound of Claim 2, further characterized by a differential scanning calorimetry thermogram substantially in accordance with that shown in FIG. 4.

Claim 7 (Currently amended). The crystalline freebase of Claim 1, wherein Form IV is further characterized by having five or more additional diffraction peaks at 2θ values selected from 10.6±0.1, 15.0±0.1, 16.0±0.1, 17.3±0.1, 17.7±0.1, 20.9±0.1, 21.4±0.1, 22.6±0.1, 24.6±0.1, and 27.8±0.1.

Claim 8 (Original). The crystalline compound of Claim 7, characterized by a powder x-ray diffraction pattern comprising diffraction peaks at 2θ values selected from 6.6±0.1, 13.1±0.1, 15.0±0.1, 17.3±0.1, 17.7±0.1, 18.6±0.1, 19.7±0.1, 20.2±0.1, 20.9±0.1, 21.4±0.1, and 22.6±0.1.

Claim 9 (Original). The crystalline compound of Claim 7, further characterized by a powder x-ray diffraction pattern in which the peak positions are substantially in accordance with the peak positions of the pattern shown in FIG. 2.

Claim 10 (Canceled).

Claim 11 (Original). The compound of Claim 7, further characterized by a differential scanning calorimetry thermogram substantially in accordance with that shown in FIG. 5.

Claim 12 (Original). A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the compound of Claim 1.

Claim 13 (Original). The composition of Claim 12, which further comprises an agent selected from β_2 adrenergic receptor agonists, steroidal anti-inflammatory agents, phosphodiesterase-4 inhibitors, and combinations thereof; wherein the crystalline form and the agent are formulated together or separately.

Claim 14 (Original). The composition of Claim 13, which comprises a β_2 adrenergic receptor agonist and a steroidal anti-inflammatory agent.

Claim 15 (Original). The compound of Claim 1 in micronized form.

Claim 16 (Currently amended). A process for preparing the crystalline freebase Form III of Claim 2, comprising contacting biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester with a solvent consisting of acetonitrile, wherein the ratio of milligrams of the ester to total milliliters of acetonitrile is about 100:1, and the acetonitrile is added in two steps.

Claim 17 (Currently amended). A process for preparing the crystalline freebase Form IV of Claim 7, comprising a) forming a seed crystal of the crystalline freebase Form III by contacting biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester with a solvent consisting of acetonitrile, wherein the ratio of milligrams of the ester to total milliliters of acetonitrile is about 100:1, and the acetonitrile is added in two steps; b) dissolving the crystalline freebase Form III in acetonitrile to form a solution; c) and adding the seed crystal to the solution.

Claim 18 (Original). A process for purifying biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester, comprising forming the compound of Claim 1.

Claims 19-20 (Canceled).

III. REMARKS

Applicants respectfully request reconsideration of this application in view of the following remarks and election.

1. STATUS OF THE CLAIMS

Claims 1, 2, 7, 16, and 17 are amended. Claims 5, 10, and 19-20 are canceled. Claims 3-4, 6, 8-9, 11-15, and 18 are unchanged.

2. SUMMARY OF THE AMENDMENTS

Claim 1 is amended to recite the melting points of each form. Support therefor can be found, for example, in Claims 5 and 10, now canceled. Claims 2 and 7 are amended to make reference to the relevant form.

Claim 16 is amended to recite that a "a solvent consisting of" acetonitrile is used. Claims 16 and 17 are amended to specify the ratio of ester to acetonitrile and that the acetonitrile is added in two steps. Support therefor can be found, for example, in example 1 and at page 8, lines 9-11 of the Specification.

Claims 19-20, directed to the non-elected invention of Group II are canceled.

The cancellation of claims should not be construed as abandonment of any originally claimed subject matter. Accordingly, the cancellation of claims herein is without prejudice to further prosecution in a continuation, continuation-in-part, divisional or other related application. No new matter has been added.

3. REJECTION UNDER 35 U.S.C. §102(b) OVER U.S. PUBLICATION 2005/0203133

Claims 1-6, 12-16, and 18 stand rejected under 35 U.S.C. §102(b) as being anticipated by U.S. Patent Publication 2005/0203133 to Mammen et al. (hereinafter "Mammen '133").

The Examiner argues that Mammen '133 teaches the preparation of a freebase crystal using acetonitrile. The Examiner acknowledges that Mammen '133 does not describe a crystalline freebase characterized by a PXRD comprising diffraction peaks at 2θ values of 6.6±0.1, 13.1±0.1, 18.6±0.1, 19.7±0.1, and 20.2±0.1. However, the Examiner argues that the presently claimed process is the same as that disclosed by Mammen '133 and therefore it would have been expected that, without sufficient evidence to the contrary, the freebase crystal disclosed by Mammen '133 is the same as that being presently claimed.

In this, the Examiner is mistaken. One freebase form in Mammen '133 is prepared by a method that uses water as part of a solvent mixture as the inert diluent, for example a water:acetonitrile (1:1) solution (page 21, ¶304, line 2). A second freebase form in Mammen '133 is prepared by a method that uses a combination of acetonitrile and methyl *t*-butyl ether (page 22, ¶308, line 2).

Form III in the present application is prepared using the amorphous ester starting material and acetonitrile alone, with no water or other co-solvent present (page 8, lines 7-13 and Example 1 on page 27). Claim 16 has been amended accordingly.

Anticipation requires that the claimed freebase be actually disclosed in the art. The argument that the claimed freebase may have been produced by the Mammen '133 is insufficient to support this rejeciton. Particularly because the evidence points to the contrary. There is no suggestion, and certainly no evidence that any product produced in Mammen '133 is the same as that being claimed here. The Examiner is incorrect in arguing that "it would have been expected" that the freebase disclosed by Mammen et al. would have been characterized by diffraction peaks at 2θ values of 6.6±0.1, 13.1±0.1, 18.6±0.1, 19.7±0.1, and 20.2±0.1.

The Examiner's attention is directed to WO 2006/099165 to Axt al. (hereinafter "Axt '165"). In viewing this reference in combination with Mammen '133, it is apparent that repeating the examples of Mammen '133 does not in fact result in either of the presently claimed crystalline forms. The analytical data provided in Axt '165 establishes that the forms described therein, Forms I and II, are different from the presently claimed Forms III and IV. The example in Axt '165 preparing Form I (Example 10) is identical to the example in Mammen '133 for preparing an unidentified freebase form (Example 1D). Thus, the crystalline products can reasonably be presumed to be the same form. Similarly, the example in Axt '165 for preparing Form II (Example 11) is identical to the example in Mammen '133 for preparing an unidentified freebase form (Example 1E). There is no technical basis to assume that the freebase forms, whose synthesis is described in Mammen '133, are anything other than Forms I and II. The table below provides a side-by-side comparison of the Axt '165 and Mammen '133 examples, with the relevant steps and reagents in bold text.

Axt '165: Example 10 on page 37	Mammen '133: Example 1D on page 48
230 mg of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl) benzoyl] methylamino}ethyl)piperidin-4-yl	**230 mg** of the product of Example 1 was **dissolved in 0.2 ml of H_2O:ACN (1:1)**, using slight heat. The mixture was then **heated in a**

ester (prepared as described in Example 1) was **dissolved in 0.2 ml of H_2O:ACN (1:1),** using slight heat. The mixture was then **heated in a 70 °C water bath for 2 hours**. The heat was turned off and the mixture was **allowed to cool to room temperature, then refrigerated at 4 °C for 1 hour**. **50 µl of water was then added** (oiled out), followed by the **addition of 40 µl of ACN** to get the sample back into solution. **Seeds** (crystalline material from Example 8) **were added** under slow stirring at room temperature. Crystals started to form ,and the mixture was allowed to sit overnight, with slow stirring. The next day, **a heat cool cycle was applied** (30 °C for 10 minutes, 40 °C for 10 minutes, then 50 °C for 20 minutes). The heat was turned off and the mixture allowed to cool overnight, with slow stirring. The next day, **a second heat/cool cycle was applied** (60 °C for 1 hour, with dissolving observed at 70 °C). The heat was turned off and the mixture allowed to cool overnight, with slow stirring. The next day, crystals were present and **a third heat cool cycle was applied** (60 °C for 3 hours). The heat was turned off and the mixture allowed to cool overnight, with slow stirring. The next day, **a heat cool cycle was applied** (60 °C for 3 hours, slow cool, then 60 °C for 3 hours). The heat was turned off and the mixture allowed to cool overnight, with slow stirring. **After 3 days, the solid was filtered** and placed on a high vacuum line to remove all solvent and give the title compound.	**70°C water bath for 2 hours**. The heat was turned off and the mixture was **allowed to cool to room temperature, then refrigerated at 4°C for 1 hour**. **50 µl of water was then added** (oiled out), followed by the **addition of 40 µl of ACN** to get the sample back into solution. **Seeds** (synthesis described below) **were added** under slow stirring at room temperature. Crystals started to form ,and the mixture was allowed to sit overnight, with slow stirring. The next day, **a heat cool cycle was applied** (30°C for 10 minutes, 40°C for 10 minutes, then 50°C for 20 minutes). The heat was turned off and the mixture allowed to cool overnight, with slow stirring. The next day, **a second heat/cool cycle was applied** (60°C for 1 hour, with dissolving observed at 70°C). The heat was turned off and the mixture allowed to cool overnight, with slow stirring. The next day, crystals were present and **a third heat cool cycle was applied** (60°C for 3 hours). The heat was turned off and the mixture allowed to cool overnight, with slow stirring. The next day, **a heat cool cycle was applied** (60°C for 3 hours, slow cool, then 60°C for 3 hours). The heat was turned off and the mixture allowed to cool overnight, with slow stirring. **After 3 days, the solid was filtered** and placed on a high vacuum line to remove all solvent and give a freebase crystal of the title compound.
Axt '165: Example 11 on page 38	Mammen '133: Example 1E on page 49
70 mg of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl] methylamino}ethyl)piperidin-4-yl ester (prepared as described in Example 1) was **dissolved in 0.1 mL ACN**. **After addition of 0.3 ml MTBE**, the solution appeared cloudy. **An additional 50 µl of ACN** was added to clarify the solution (155 mg/ml ACN:MTBE = 1:2). The mixture was left in the vial and capped. Crystals appeared by the next day. **The solid was then filtered** and placed on a high vacuum line to remove all solvent and give the title compound.	**70 mg** of the product of Example 1 **was dissolved in 0.1 mL ACN**. **After addition of 0.3 ml MTBE**, the solution appeared cloudy. **An additional 50 µl of ACN was added** to clarify the solution (155 mg/ml ACN:MTBE = 1:2). The mixture was left in the vial and capped. A solid appeared by the next day. **The solid was then filtered** and placed on a high vacuum line to remove all solvent and give a freebase crystal of the title compound.

This table establishes that the procedures described in Mammen '133 would NOT have yielded the presently claimed compounds. In fact, the Mammen '133 procedures yielded the compounds described in Axt '165 (freebase Forms I and II), which are patentably distinct from the presently claimed Forms III and IV.

Accordingly, Applicants submit that Claims 1-6, 12-16, and 18 are allowable over Mammen '133 and respectfully request that the rejection of these claims under 35 U.S.C. §102(b) be withdrawn.

4. REJECTIONS UNDER 35 U.S.C. §103(a)

A. REJECTION OVER US 2005/0203133

Claims 1, 7-11, and 17 stand rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent Publication 2005/0203133 to Mammen et al. (hereinafter "Mammen '133").

Claim 17 has been amended to more specifically recite the steps involved in preparing the crystalline forms. Such steps are not suggested by Mammen '133.

As noted above, "Axt '165" provides analytical data for the crystalline forms prepared in Mammen '133. In viewing this reference in combination with Mammen '133, it is apparent that repeating the examples of Mammen '133 does not in fact resulting in either of the presently claimed crystalline forms. The analytical data provided in Axt '165 establishes that the forms described therein, Forms I and II, are different from the presently claimed Forms III and IV.

In addition, Claim 1 has now been amended to recite the melting points of Forms III and IV: 125°C and 119°C, respectively. Page 1, line 26 to page 2, line 8 of the Specification states that therapeutic agents useful for treating pulmonary disorders are preferably administered using an inhalation device. It is important to note that when preparing formulations for use in such devices, it is desirable to utilize a crystalline form that has a relatively high melting point, which allows the material to be micronized without significant decomposition. It is further noted that crystalline freebase forms I and II were previously reported (citing the US equivalent of Axt '165), but that the freebase forms of the present invention have different and particularly useful properties, including higher melting points.

Page 14, lines 2-5 of Axt '165 describes the melting points of freebase forms I and II:

> "[A] crystalline freebase (Form I) is characterized by its DSC trace which showed a maximum endothermic heat flow at about **102.7°C**, as illustrated in FIG. 19; and a crystalline freebase (Form II) is characterized by its DSC trace which showed a maximum endothermic heat flow at about **98.6°C**, as illustrated in FIG. 24." {emphasis added}

The higher melting points of the presently claimed Forms III and IV provide a substantiated and unexpected property, which is very relevant for its technical application. It is indeed surprising that these later discovered polymorphs have significantly higher melting points than the earlier discovered freebase Forms I and II. This serves to refute the obviousness rejection.

Accordingly, Applicants submit that Claims 1, 7-11, and 17 are allowable over Mammen '133 and respectfully request that the rejection of these claims under 35 U.S.C. §103(a) be withdrawn.

B. REJECTION OVER WO 2006/099165

Claims 1-18 stand rejected under 35 U.S.C. §103(a) as being unpatentable over WO 2006/099165 to Axt al. (hereinafter "Axt '165").

The present invention describes two freebase forms, Forms III and IV. Axt '165 describes freebase forms, Forms I and II. The presently claimed materials are different based upon the PXRD peaks and the melting points. The process claims have been amended to specify ratios and steps that further distinguish from the methods described in Axt '165.

The Examiner argues that it would have been obvious that the products resulting from Axt '165 would be the presently claimed materials. That is simply incorrect and completely disregards the fact that the Axt '165 products, designated Forms I and II, have different PXRD profiles AND different melting points from the presently claimed materials.

The Axt '165 reference does not provide a reasonable expectation of success for making a different polymorph, let alone either of the two specific polymorphs being claimed. The Examiner has not adequately shown that the cited reference would have led one skilled in the art to make the claimed crystalline forms and therefore, the cited reference does not support a *prima facie* case of obviousness. Withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

5. NON-STATUTORY OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTIONS

Claims 1-18 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over:

Claims 1 and 3-5 of U.S. Patent No. 7,585,879;

Claims 1-9 and 12-30 of U.S. Patent No. 7,803,812;

Claims 1-14 of U.S. Patent No. 8,273,894;

Claim 1 of U.S. Patent No. 8,034,946;

Claims 1-4 of U.S. Patent No. 7,910,608;

Claims 1-5, 7, and 9-22 of U.S. Patent No. 7,550,595; and

Claims 13-14 of U.S. Patent No. 7,288,657.

These are referred to collectively as the "Cited Patents."

The Examiner argues that the Cited Patents teach that biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoyl piperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester can exist as a freebase crystal. The Examiner then argues that it would be obvious that the claims of the Cited Patents would encompass the presently claimed materials.

It is well established in the pharmaceutical arts that the formation of crystalline compounds is unpredictable. The unpredictability of this art has even been recognized by the courts. The lower court in Sanofi-Synthelabo v. Apotex, Inc., 492 F. Supp.2d 353, 374 (S.D.N.Y. 2007) had observed that the scientific literature listed eighty acids as candidates for forming salts with basic drug compounds, fifty-three of which had been used in FDA-approved drugs. However, the experts of both parties (and the court) agreed that whether a pharmaceutically suitable crystalline salt will form from a particular acid-base combination remains unpredictable. Therefore, whether a crystalline material will form in a particular reaction of acid and base, the type of crystalline material that will form, and the properties that the crystalline material will have, are all unpredictable. This level of unpredictability does not change because it was known that the compound crystallized in different freebase forms (as described in the Cited Patents).

A proper obviousness-type double patenting rejection rests on the fact that a patent has been issued and later issuance of a second patent will continue protection, beyond the date of expiration of the first patent, of a mere variation of that invention which would have been obvious to those of ordinary skill in the relevant art (*In re Kaplan*, 789 F.2d 1574, Fed. Cir.

1986). That being the case, there must be some clear evidence to establish why the variation would have been obvious which can properly qualify as prior art. Even if obviousness of the variation is predicated on the level of skill in the art, prior art evidence is needed to show what that level of skill was at the time of the invention. The Examiner has not provided evidence which would establish that pending Claims 1-18, which require two particular crystalline forms, would have been obvious over the freebase crystals described in the Cited Patents.

One skilled in the art in possession of a freebase crystal would not have been able to predict whether the compound would also form other freebase crystalline materials, and in particular, would have had no way to predict whether the compound would form crystalline materials with the properties recited in the present claims. The Cited Patents do not provide a reasonable expectation of success for making a different crystalline form, let alone the two specific forms that are being claimed by Applicants. Absent a showing of predictability, a *prima facie* case of obviousness cannot be supported.

The Examiner is reminded that the presently claimed crystalline materials have unobvious and superior properties. It is recognized in the art that it is desirable to have a crystalline form that has a relatively high melting point. Such elevated melting temperatures allow the material to be processed, for example, micronized, without significant decomposition. It has been established that the freebase materials described in the Cited Patents are those set forth in Axt '165, where Form I is characterized by a melting point of about **102.7°C** and Form II is characterized by a melting point of about **98.6°C.** The presently claimed crystalline forms have higher melting points: Form III has a melting point of about **125°C** and Form IV has a melting point of about **119°C**, both of which are significantly higher than those in Axt '165 (and thus in those in the Cited Patents).

Finally, the Examiner has taken the position that although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter embraced in the instant claims is also embraced in the Cited Patents. It is submitted that the Examiner is improperly confusing domination with double patenting.

In Ex parte Engel, Appeal No. 2008-0406, August 29, 2008, the Board of Patent Appeals and Interferences overturned an obviousness-type double patenting rejection in an application to a crystalline difumarate salt of a chemical compound where the reference patent claimed a salt of the compound:

> There is no dispute that the patented claims are generic to claim 3 [to the crystalline difumarate salt] of the application and would dominate claim 3 of the application, in that claim 3 could not be practiced without infringing the patented claims. But domination, "by itself, does not give rise to 'double patenting'." In re Kaplan, 789 F.2d 1574, 1577 (Fed. Cir. 1986) [229 U.S.P.Q. 678]; see also In re Sarett, 327 F.2d 1005, 1014 (C.C.P.A., 1964) [140 U.S.P.Q. 474].

In re Sarett, referenced in the B.P.A.I. opinion, specifically counsels:

> it is elementary that readability of a claim on the subject matter of another claim (domination) is neither determinative of the double patenting issue nor demonstrative that claims are directed to the same invention" In re Sarett, 140 U.S.P.Q. 474, 482

Thus, the courts and the B.P.A.I. have rejected the reasoning of the present Office Action, these decisions have held that an obviousness-type double patenting rejection to a species claim cannot be based on a generic claim in a patent.

Accordingly, Claims 1-18 are not obvious in view of any of the Cited Patents and Applicants respectfully request that the obviousness-type double patenting rejection be withdrawn.

6. CONCLUSION

The above arguments and amendments to the Claims are submitted for the purpose of facilitating allowance of the Claims.

A sincere effort has been made to place this application in condition for allowance, and an early notice of allowance is earnestly requested. If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney for Applicants at (650) 808-4010.

Respectfully submitted,
THERAVANCE, INC.

Date: February 27, 2013 By: /Shelley Eberle/
Shelley Eberle
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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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NOTICE OF ALLOWANCE AND FEE(S) DUE

27038 7590 05/28/2013

THERAVANCE, INC.
901 GATEWAY BOULEVARD
SOUTH SAN FRANCISCO, CA 94080

EXAMINER	
PIHONAK, SARAH	
ART UNIT	PAPER NUMBER
1627	

DATE MAILED: 05/28/2013

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/835,964	07/14/2010	Grahame Woollam	P-257-US1	1229

TITLE OF INVENTION: CRYSTALLINE FREEBASE FORMS OF A BIPHENYL COMPOUND

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1780	$300	$0	$2080	08/28/2013

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax **(571)-273-2885**

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

27038 7590 05/28/2013
THERAVANCE, INC.
901 GATEWAY BOULEVARD
SOUTH SAN FRANCISCO, CA 94080

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/835,964	07/14/2010	Grahame Woollam	P-257-US1	1229

TITLE OF INVENTION: CRYSTALLINE FREEBASE FORMS OF A BIPHENYL COMPOUND

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1780	$300	$0	$2080	08/28/2013

EXAMINER	ART UNIT	CLASS-SUBCLASS
PIHONAK, SARAH	1627	514-279000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:

❑ Issue Fee
❑ Publication Fee (No small entity discount permitted)
❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**

❑ A check is enclosed.
❑ Payment by credit card. Form PTO-2038 is attached.
❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

PTOL-85 (Rev. 02/11)

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29	NOTE: Absent a valid certification of Micro Entity Status (see form PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
❑ Applicant asserting small entity status. See 37 CFR 1.27	NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
❑ Applicant changing to regular undiscounted fee status.	NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/835,964	07/14/2010	Grahame Woollam	P-257-US1	1229

27038 7590 05/28/2013

THERAVANCE, INC.
901 GATEWAY BOULEVARD
SOUTH SAN FRANCISCO, CA 94080

EXAMINER	
PIHONAK, SARAH	
ART UNIT	PAPER NUMBER
1627	

DATE MAILED: 05/28/2013

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 335 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 335 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	12/835,964	WOOLLAM, GRAHAME	
	Examiner	Art Unit	
	SARAH PIHONAK	1627	

All participants (applicant, applicant's representative, PTO personnel):

(1) *SARAH PIHONAK*. (3)_____.

(2) *SHELLEY EBERLE*. (4)_____.

Date of Interview: *14 May 2013*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☒Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *1-4,6-9,11-17,21-24*.

Identification of prior art discussed: *Mammen et. al.; Axt et. al.*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

A proposed examiner's amendment was approved by Shelley Eberle on behalf of the Applicants. Claims 2, 8, and 18 are deleted by examiner's amendment, and claims 1, 3-4, 6-7, 9, 11-17, and newly added claims 21-24 are allowed.

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/S. P./ Examiner, Art Unit 1627	

Notice of Allowability	Application No. 12/835,964	Applicant(s) WOOLLAM, GRAHAME	
	Examiner SARAH PIHONAK	Art Unit 1627	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *2/27/2013*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *1,3-4,6-7,9,11-17,21-24*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov .
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

   Interim copies:

   a) ☐ All b) ☐ Some c) ☐ None of the: Interim copies of the priority documents have been received.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☒ Interview Summary (PTO-413), Paper No./Mail Date *5/14/2013* .
5. ☒ Examiner's Amendment/Comment
6. ☒ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/S. P./
Examiner, Art Unit 1627

DETAILED ACTION

Priority

This application, filed on 7/14/2010, claims priority to provisional appl. 61/225803, filed on 7/15/2009. The effective U.S. filing and priority date of the claims is 7/15/2009.

Response to Remarks

1. Claims 1-4, 6-9, and 11-18 are pending as of the reply and amendments filed on 2/27/2013.

The rejection under 35 USC 102(b) as being anticipated by Mammen et. al., US Patent Publ. 2005/0203133, is withdrawn in consideration of the claim amendments.

Applicant's arguments, and the claim amendments with respect to the rejection under 35 USC 103(a) as being unpatentable over Mammen et. al., US Patent Publ. 2005/0203133, have been fully considered and are found persuasive. The rejection under 35 USC 103(a) as being unpatentable over Mammen et. al., is withdrawn.

Applicant's arguments, and the claim amendments with respect to the rejection under 35 USC 103(a) as being unpatentable over Axt et. al., WO 2006/099165, have been fully considered and are found persuasive. The rejection under 35 USC 103(a) as being unpatentable over Axt et. al., is withdrawn.

Applicant’s arguments with regards to the rejections for obviousness type double patenting over the claims of USP 7,585,879; USP 7,803,812; USP 8,273,894; USP

8,034,946; USP 7,910,608; USP 7,550,595; and USP 7,288,657, have been fully considered and are found persuasive. The rejections for obviousness type double patenting are withdrawn.

2. A proposed examiner's amendment was approved by the Applicant's representative, which will be disclosed in the office action. Claims 1, 3-4, 6-7, 9, 11-17, and 21-24 are allowed. A statement of reasons for allowance is also disclosed.

Examiner's Amendment

3. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Shelley Eberle on 5/14/2013.

Please amend the claims accordingly:

4. For claim 1, line 4, after "20.2±0.1,", **delete** "and selected from Form III having a melting point of about 125°C and Form IV having a melting point of about 119°C", and **insert** "and further characterized by having five or more additional diffraction peaks at 2θ values selected from 8.8±0.1, 10.1±0.1, 11.4±0.1, 11.6±0.1, 14.8±0.1, 15.2±0.1, 16.1±0.1, 16.4±0.1, 16.9±0.1, 17.5±0.1, 18.2±0.1, 19.3±0.1, 19.9±0.1, 20.8±0.1, 21.1±0.1, 21.7±0.1, and 22.3±0.1; designated as Form III; and having a melting point of about 125°C".

5. Delete claim 2.

6. For claim 3, line 1, after "Claim", **delete** "2", and **insert** "1".

7. For claim 4, line 1, after "Claim", **delete** "2", and **insert** "1".

8. For claim 6, after "Claim", **delete** "2", and **insert** "1".

9. For claim 7, line 1, **delete** "The crystalline freebase of Claim 1, wherein Form IV is", and **insert** "A crystalline freebase of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester characterized by a powder x-ray diffraction comprising diffraction peaks at 2θ values of 6.6±0.1, 13.1±0.1, 18.6±0.1, 19.7±0.1, and 20.2±0.1, and".

10. For claim 7, line 4, after "27.8±0.1", **insert** "; designated as Form IV; and having a melting point of about 119°C".

11. Delete claim 8.

12. For claim 16, line 2, after "Claim", **delete** "2", and **insert** "1".

13. Delete claim 18.

14. Add claim 21, which is: "A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the compound of Claim 7."

15. Add claim 22, which is: "The composition of claim 21, which further comprises an agent selected from $ß_2$ adrenergic receptor agonists, steroidal anti-inflammatory agents, phosphodiesterase-4 inhibitors, and combinations thereof; wherein the crystalline form and the agent are formulated together or separately."

16. Add claim 23, which is: "The composition of claim 22, which comprises a $ß_2$ adrenergic receptor agonist and a steroidal anti-inflammatory agent."

17. Add claim 24, which is: "The compound of Claim 7 in micronized form."

Reasons for Allowance

18. The following is an examiner's statement of reasons for allowance: there is no prior art which teaches or suggests biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester in crystalline freebase form III or form IV, with the characteristic x–ray diffraction peaks as cited in the claims, having a melting point of about 125°C (for form III), or a melting point of about 119°C (for form IV). The closest prior art is taught by Mammen et. al., US Patent Publ. 2005/0203133, and Axt et. al., WO 2006/099165 (both of prior record). Mammen et. al. teaches freebase crystalline biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester prepared by dissolving the freebase in a mixture of acetonitrile and water; however, Mammen et. al. does not disclose that the compound has x-ray diffraction peaks of 2θ values of 6.6±0.1, 13.1±0.1, 18.6±0.1, 19.7±0.1, and 20.2±0.1, or the melting points of Form III or Form IV as cited in the instant claims. The Applicants have shown that crystalline forms III and IV of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester as claimed are prepared with a solvent consisting of acetonitrile, and not a mixture of acetonitrile and water, as taught by Mammen. The Applicants have shown that the procedure for preparing freebase crystalline biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester as taught by Mammen is

identical to the procedure for preparing crystalline freebase form II of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester as taught by Axt. Therefore, the crystalline forms III and IV of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester are novel and non-obvious over Mammen et. al.

Axt et. al. teaches crystalline freebase biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester; however, the x-ray diffraction peaks of the compound as taught by Axt et. al. differ from those of crystalline forms III and IV as currently cited in the instant claims. Additionally, the crystalline freebase forms of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester as taught by Axt et. al. are identified as having melting points of 102.7℃, and 98.6℃, which are considerably lower than the melting points of crystalline forms III and IV as cited in the instant claims. Crystalline forms III and IV of freebase biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester are novel and non-obvious over Axt et. al.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled “Comments on Statement of Reasons for Allowance.”

Conclusion

19. Claims 1, 3-4, 6-7, 9, 11-17, and 21-24 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARAH PIHONAK whose telephone number is (571)270-7710. The examiner can normally be reached on Monday-Friday 8:00 AM - 5:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. P./

Examiner, Art Unit 1627

/SREENI PADMANABHAN/
Supervisory Patent Examiner, Art Unit 1627